REMARKS

Petition for Extension of Time Under 37 CFR 1.136(a)

It is hereby requested that the term to respond to the Examiner s Action of January 9, 2008 be extended three months, from April 9, 2008 to July 9, 2008.

Authorization to charge a Credit Card is given to cover the extension fee. The Commissioner is hereby authorized to charge any additional fees associated with this communication to Deposit Account No. 19-5425.

Reconsideration of the present application in view of the above amendments and the following remarks is requested respectfully.

Discussion of the Claims

Claims 1-63 are pending. The Examiner indicates that Claims 4-7, 9, 11-19 and 26-56 have been withdrawn as being drawn to either a non-elected species or a non-elected invention, and indicates that Claims 1-3, 8, 10 and 20-25 are being examined on the merit.

Applicant, however, submits that only Claims 12-19 and 26-56 have been previously withdrawn, and that Claims 57 and 58 were added in the previous Reply, filed on October 19, 2007. Claims 59-63 are added. Accordingly, Claims 1-11, 20-25, and 57-63 are presented for examination.

Clarification of the pending claim status is respectfully requested. For the purposes of this Reply, Applicant will present amendments and arguments based upon Applicant s stated pending claims.

Discussion of Amendments

Claim 8 was amended to recite 'wherein, other than the motif, the variant has at least 9 identical amino acids to the albumin secretion pre sequence.α Support for this amendment can be found, for example, in the specification at page 19, lines 11-16.

Claim 22 was amended to recite 'wherein the variant comprises an amino acid sequence that is at least 90% identical to albumin.α Support for this amendment can be found, for example, in the specification at page 9, lines 11-15.

Claims 59-63 were added to claim specific secretion pre sequences. Support for these claims can be found, for example, in the specification at page 2, lines 6-12; and page 19, lines 11-16.

Summary of the Examiner s Action

On pages 2 and 3 of the Office Action, the Examiner indicated that the previously-issued rejection of Claims 1 and 21-25 stand rejected under 35 U.S.C. § 101 has been withdrawn.

Similarly, on page 3 of the Office Action, the Examiner has indicated that the previous rejection of Claims 1, 3, 6, 8, 10 and 20-23 under 35 U.S.C. §102 has been withdrawn.

Claims 1-3, 8, 10, and 20-25 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

Claims 1 and 21-25 are rejected under 35 U.S.C. §101 as being directed to non-statutory subject matter.

Claims 1-3, 8, 20-22 and 24 are rejected under 35 U.S.C. § 102(b) as being anticipated by International Application No. WO 01/64834 to Tang et al.

Election/Restriction

The Examiner has indicated that elected species SEQ ID NO: 28 has been found free of art. The Examiner has withdrawn Claims 4, 5-7, 9, and 11 as being drawn to a non-elected species. Applicant respectfully disagrees. The elected species SEQ ID NO: 28 is specifically recited in Claim 11 and encompassed by Claims 4-7 and 9. Accordingly, it is not understood why Claim 11 would not be drawn to the elected species or why Claims 2-3 and not Claims 4-7 and 9. Moreover, as discussed during the Examiner Interview conducted on October 17, 2007, if Claim 1 is free of the art (as discussed below), the Examiner agreed to consider the patentability of Claims 2, 4, 5, 7, and 9.

Discussion of the Applicant s Invention

Claim 1 and its dependent claims are directed to a polypeptide comprising a leader sequence which comprises a pre sequence and the X_1-X_2-X_3-X_4-X_5 motif as defined in the claim,

and a mature protein. Applicant has unexpectedly found that the yield of secreted protein can be increased by providing the recited amino acid sequence motif in the leader sequence. New Claims 59-63 are directed to polypeptides of the claimed invention with particular secretion pre sequences.

Claim 57 is directed to the leader sequence of Claim 1, and Claim 58 is directed to the particular elected species.

Written Description Rejection

The Examiner has rejected claims 1-3, 8, 10 and 20-25 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner asserts that 'the claim does not recite the nature of the leadr sequence , pre sequence or the protein heterologous to the leader sequence in terms of the amino acid sequences that would properly define each of these different peptidesα and 'that the claims do not adequately provide structural characteristicsα for these elements.

The written description requirement does not require a description of the complete structure of every species within a chemical genus. *See Utter v. Hiraga*, 845 F.2d 993, 998 (Fed. Cir. 1988). In *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 1316, 1324 (Fed. Cir. 2002), the Federal Circuit made clear that the written description requirement can be satisfied in a number of ways by disclosing, for example, 'complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between

function and structure, or some combination of characteristics.α *See* M.P.E.P. § 2163.

The Examiner has the burden of establishing 'a *prima facie* case by providing reasons why a person skilled in the art at the time the application was filed would not have recognized that the inventor was in possession of the invention as claimed in view of the disclosure of the application as filed. A general allegation of 'unpredictability in the artα is not a sufficient reason to support a rejection for lack of adequate written description.α M.P.E.P. § 2163.04.

Here, Applicant s claims are directed to a polypeptide comprising (i) a leader sequence and (ii) a mature protein. The leader sequence comprises (a) a secretion pre sequence and (b) the defined -X_1-X_2-X_3-X_4-X_5- motif. One of skill in the art would recognize that applicant was in possession of each of these elements and the claimed invention as a whole at the time of filing.

Claimed Motif

Applicant has provided *the complete structure* of the crucial element of the claimed invention the -X_1-X_2-X_3-X_4-X_5- motif. The -X_1-X_2-X_3-X_4-X_5- motif is recited in the application and includes a limited combination of amino acids. The -X_1-X_2-X_3-X_4-X_5- motif is defined structurally in Claim 1 as a combination of five amino acids where X_1 is phenylalanine, tryptophan, or tyrosine, X_2 is isoleucine, leucine, valine, alanine or methionine, X_3 is leucine, valine, alanine or methionine, X_4 is serine or threonine and X_5 is isoleucine, valine, alanine or methionine. Accordingly, the specification adequately describes the claimed motif.

To the extent that the Examiner is arguing that Applicants were not in possession of all the claimed variants, Applicant submits that it was reasonable to predict at the time of filing that all

claimed variants would achieve the inventive effect. The data submitted with the attached Declaration of Darrell Sleep shows that claimed variants of FIVSI achieve the same inventive effect as FIVSI itself.

An extensive study was conducted to determine the effect of various conservative substitutions of the FIVSI motif (as defined by Claim 1) at each of its positions. In particular, Applicants tested the ability of the motif within the context of a leader sequence to enhance expression of a recombinant heterologous protein (the protein chosen to illustrate this was recombinant, human albumin; 'rHAα). In addition, the effect of repositioning the motif within the leader sequence has also been tested. The enclosed data demonstrate that claimed variants retain the beneficial effect of the FIVSI motif. Sleep Declaration at ¶ 5.

As supported by the attached data, a motif having one of the defined conservative substitutions at any one of its five positions shares the inventive features of FIVSI, in that it supports an enhanced production of recombinant protein. Given that the conservative substitutions as defined by Claim 1 are acceptable at any position, there is no reason to suspect that a motif having more than one of the conservative substitutions as defined by Claim 1 would not also retain the inventive technical effect of FIVSI. Accordingly, one of skill in the art would consider that Applicant were in possession of the full scope of the motif as claimed.

Furthermore, Figure 2 from the attached declaration shows the precise location of the pentapeptide motif within the pre sequence is not essential for the beneficial effect. Where the FIVSI motif occupies positions ' 17 to ' 21 of the leader sequence as a result of the introduction

of an additional isoleucine residue within the leader sequence (i.e. 'FIVSI+Iα), compared to the '16 to '20 position as exemplified in Figure 1 of the description, high level rHA production is retained. The positioning of the motif at '16 to '20 is indicated in the description at page 19, lines 18-21 to be merely a *preferred embodiment* for the motif s positioning; there is no suggestion that other positions would be unacceptable.

Moreover, results comparing the rHA production of FIVSI at '17 to '21 and IIVSI at '17 to '21, show that the latter motif, which contains a non-conservative substitution at position 1, i.e. a substitution that is *outside of the scope of the claims*, is *less effective* at promoting high level rHA production. In fact, not only does the non-conservative substitution result in a motif that is less effective than FIVSI, it also produces a motif that is less effective than the wild-type sequence SFISL. This result shows that the benefit of the present invention cannot be obtained by simply introducing *any* hydrophobic amino acid in place of one or more of the FIVSI residues; on the contrary the data presented demonstrate that the Applicant has described a limited number of amino acids for use in a motif that provide a clear inventive effect.

Secretion Pre Sequence

The Examiner asserts that 'it is unclear from the claim as recited what is the nature and composition of . . . the secretions pre sequence . . . in terms of its amino acid sequence that would provide structural aspect to these sequences.α Action at page 6.

First, Applicants note that Claim 11 recites a specific secretion pre sequence in terms of its amino acid sequence. Accordingly, there can be no doubt that Claim 11 satisfies the written description requirements.

Second, Claim 8 was amended to recite 'wherein, other than the motif, the variant has at least 9 identical amino acids to the albumin secretion pre sequence.α Accordingly, claim 8 and its dependent claims 9 and 10 are directed to an albumin secretion pre sequence or a variant that has at least 9 identical amino acids to the albumin secretion pre sequence. Accordingly, all of the secretion pre sequences share at least 9 of the remaining 13 amino acids of the albumin secretion pre sequence. See Figure 1. In view of this disclosure, those skilled in the art could readily envision all of the species of the claimed genus, and thus, the specification satisfies the written description requirement with respect to at least these Claims 9 and 10. *See, e.g., Written Description Training Materials*, March 25, 2008 at Example 10 (claim 2); *see also Ex parte Bandman*, Appeal No. 2004-2319 at p. 5 (BPAI 2005).

Third, those skilled in the art would recognize that the FIVSI motif would have a beneficial effect on protein secretion without limitation to any particular leader sequence or secretion pre sequence. In support, Applicant has submitted the data shown in Figure 3 of the attached declaration. As can be seen from Figure 3, where the invertase leader sequence responsible for secretion of rTF contained FIVSI (i.e. plasmid pDB3606), production of rTF was greater than that from the control yeast strain in which the invertase leader sequence contained the prior art motif SFISL (i.e. plasmid pDB3221). Sleep Declaration at ¶ 15. The data show that the

beneficial effect of including FIVSI in a leader sequence is not limited to improving secretion of a desired protein in the context of a modified albumin secretion pre sequence, but extends to improving secretion in the context of other pre sequences, such as a modified invertase pre sequence. Sleep Declaration at ¶ 16. Accordingly, as the identity of the leader sequence and secretion pre sequence is not relevant to the patentability of the pending claims (excluding the FIVSI motif), the written description rejection based on these grounds should be withdrawn.

Finally, the written description rejection should not be applied to new Claims 59-63 at least on this ground. Claims 59-63 are directed to specific secretion pre sequences and variants thereof.

Mature Desired Protein

The Examiner again asserts that 'it is unclear from the claim as recited what is the nature and composition of . . . the nature of the mature desired protein in terms of its amino acid sequence that would provide structural aspect to these sequences.α Action at page 6.

The term 'mature desired proteinα is defined as the secreted protein without its secretion pre sequence or the pre-pro sequence. See page 18, lines 21-25 and page 42, lines 8-11. As with the leader sequence and secretion pre sequence, the identity of the mature desired protein is not relevant to the patentability of the pending claims.

Applicant first notes that claims 57 and 58 are directed to the only the leader sequence of the present invention and do not recite 'a mature desired protein.α Claim 58 recites the specific elected species of SEQ ID NO:28. Accordingly, to the extent that the Examiner s rejection is

maintained on these grounds alone, the written description rejection should not be applied to claims 57 and 58.

Those of skill in the art would recognize from the disclosure of the present application that the inventive effect of the leader sequence in improving secretion of the desired protein is independent of the identity of the desired protein.

It is well established that leader sequences can direct the secretion of desired proteins independently of the identity of the desired protein. Please see Gierasch, 1989, *Biochemistry*, **28**(3), 923-931 (submitted to USPTO in response dated 19 October 2007) which states that '

> Recombinant proteins composed of a signal sequence from one organism and a mature secretory protein from another organism are frequently export competent (page 923, left column, first paragraph).
>
> The fact that they [i.e. signal sequences] can in many instances be transferred from one protein to another and still function implies that they act quite independently of their context (the sequences adjacent). Signal sequences perform their multiple roles while they are attached as N-terminal extensions on their cognate mature proteins; yet they are probably relatively free of interactions with the rest of the nascent chain (page 927, left column, final sentences; emphasis added).

Based on the knowledge in the field of leader sequences, illustrated by the above passages, in combination with the disclosure of the application, those skilled in the art would predict at the date of filing that the leader sequence as defined in claim 1 would improve secretion of any desired protein, and not just of albumin.

As can be seen from Figure 3, where the HSA leader sequence responsible for secretion of rTF contained FIVSI (i.e. plasmid pDB3205), production of rTF was greater than that from the control yeast strain in which the HSA leader sequence contained the prior art motif SFISL (i.e. plasmid pDB3605). Sleep Declaration at ¶ 15. The data show that the beneficial effect of including FIVSI in a leader sequence is not limited to improving secretion of albumin as a desired protein, but extends to improving secretion of other proteins, such as transferrin, as a desired protein. Sleep Declaration at ¶ 16.

Accordingly, the written description rejection should be withdrawn.

Non-Statutory Subject Matter Rejection

The Examiner rejected claims 1 and 21-25 under 35 U.S.C. § 101 as being directed to non-statutory subject matter. The Examiner asserts that claim 1 'encompasses any and all native polypeptide (protein) of nature.α The Examiner further asserts that the polypeptide SEQ ID NO: 589 of Tang et al. (WO 01/64834) discloses the penta peptide motif FIASA.

SEQ ID NO: 589 of Tang et al. is a predicted amino acid sequence. According to the table on page 121, SEQ ID NO: 589 is predicted from a 'contigα (a set of overlapping DNA sequences obtained by shot-gun DNA sequencing). The predicted amino acid sequence contains FIASA (which is one of the variants encompassed by claim 1). However, FIASA follows shortly after a predicted stop codon, which suggests that it does not form part of a leader sequence for a protein. Accordingly, the Examiner has not shown that Applicant s claimed motif is found

naturally in leader sequences for proteins as recited in claim 1. Thus, SEQ ID NO: 589 can not form that basis of a non-statutory subject matter rejection.

Anticipation Rejection

The Examiner rejected claims 1-3, 8, 20-22 and 24 under 35 U.S.C. §102(b) as being anticipated by International Application No. WO 01/64834 to Tang et al.

'A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).α M.P.E.P. § 2131.

Claim 1 recites a leader sequence comprising Applicant s claimed motif. Although SEQ ID NO: 589 of Tang et al. discloses the sequence FIASI, there is no disclosure that such a sequence is found in a leader sequence as recited in claim 1. In fact, FIASA follows shortly after a predicted stop codon, which suggests that it does not form part of a leader sequence for a protein. Accordingly, this rejection should be withdrawn.

Rejected claims 2-3, 8, 20-22 and 24 are dependent from independent claim 1. Since, as discussed above, Tang et al. does not teach or suggest all the elements of claim 1, it cannot anticipate claims 2-3, 8, 20-22 and 24. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Finality of the Next Action Is Precluded

Lastly, Applicant respectfully requests that the Office confirm the status of claims 57 and 58, which was not addressed by the Office Action. Applicant respectfully submits that the Office s failure to acknowledge claims 57 and 58 precludes the finality of a next Office action rejecting those claims, because such a rejection will not have been necessitated by either a claim amendment or based on information from an information disclosure statement. (See MPEP § 706.07(a)).

Conclusion

In view of Applicant s claim amendments and the arguments presented above, the present application is believed to be in condition for allowance and an early notice thereof is earnestly solicited. Applicant requests that the Examiner contact the undersigned before issuing another action.

Respectfully submitted,

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